# Advances in Pulmonary Hypertension

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High Altitude and Pulmonary Hypertension



From the Andes to the Rocky Mountains: A Historical View of High-Altitude Pulmonary Hypertension *Christopher H. Chang, MD; Jeffrey C. Robinson, MD* 

Impact of Altitude on Cardiopulmonary and Right Ventricular Hemodynamics During Exercise *William K. Cornwell III, MD, MSCS; Andrew Lovering, PhD* 

PH Professional Network: Up, Up, and Away: Clinical Considerations for Altitude-Related Travel and Pulmonary Hypertension *Amanda Schnell Heringer, RN, MS, AGCNS-BC; Elise Hazlewood, RN, MS, CCNS* 

A Life at High Altitude: A Conversation With Todd Bull and Peter Hackett *Todd Bull, MD; Peter Hackett, MD* 

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#### **Program Description**

The mission of Advances in Pulmonary Hypertension is to serve as the premiere forum for state-of-the-art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension (PH). The 2018 Nice revision of the World Symposium on Pulmonary Hypertension (Simmonneu G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1). DOI:10.1183/13993003.01913-2018) serves as a guide to categories of PH addressed in Advances in Pulmonary Hypertension. While focusing on Group 1 PH (PAH: pulmonary arterial hypertension), the other categories (Group PH due to left heart disease; Group 3, PH due to lung diseases and/or hypoxia; Group 4, PH due to pulmonary artery obstructions; Group 5, PH with unclear and/or multifactorial mechanisms) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

#### Objectives

- Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of PH.
- Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

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Advances in Pulmonary Hypertension is directed to cardiologists, pulmonologists, rheumatologists, pediatricians, internists, and other health care professionals involved in the treatment of patients with PH.

Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned pulmonary hypertension (PH) experts with oversight by PHA's Scientific Leadership Council. The mission of Advances in PH is to assist physicians in their clinical decision-making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in peer-reviewed publications. Each article is reviewed and approved by members of the Editorial Board.

While most articles are invited by the Editorial Board, the following submissions will be considered for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
   Letters to the Editor
- Letters to the Editor
  Clinical case studies

Submitted manuscripts are reviewed by the Editorial Board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision-making.

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#### Advances in Pulmonary Hypertension's Web Platform

Advances in Pulmonary Hypertension is available at www.AdvancesinPH.org. This site offers enhanced capabilities including a dedicated DOI and cross-referencing potential, as well as other features valuable to practitioners, researchers, and educators. Registration is recommended to access all site features and benefits.

Hello, everyone. As we enter December of this year, I would like to take this opportunity to express gratitude to everyone working in healthcare and/or related to someone working in healthcare over the last nine months. This unpredictable, challenging, and life-changing year has affected our work, our homes, and our way of life in ways we are only beginning to realize. Throughout this time, however, all those involved in creating these last issues of Advances in Pulmonary Hypertension—the editorial board, guest editors, authors, and participants-have graciously volunteered time above and beyond their "day jobs" and their COVID responsibilities to make these issues successful. Thank you to all of you who have contributed. A special thanks to our incredible Managing Editor, Clarissa Nemeth, who has kept us on track, kept us organized, and kept us moving forward over the last year. Our deep appreciation also extends to Rebecca Aune, who, as PHA's outgoing Director of Quality Care and Research, was phenomenal over the last two years in helping us succeed in every way imaginable and was instrumental in transitioning us from print to online. We are thrilled to welcome Elizabeth Joseloff, PhD, the Vice President, Quality Care & Research, of PHA to Advances. Her advice and leadership have been invaluable to all of us and we look forward to the years ahead. All of our appreciation goes to the entire

PHA and all the support over the last year.

This unique issue will have a great impact on our community to the extent in which an issue can make a unique contribution compared with the existing literature in the field. I would like to thank and congratulate Dr Todd Bull, the Guest Editor, for creating this incredible compilation on altitude and pulmonary hypertension (PH).

In the first article of this issue, Drs Christopher Chang and Jeffrey Robinson, both from the Oregon Health and Science University, discuss what we know about high-altitude pulmonary hypertension (HAPH). The authors describe the history behind the discovery and the early investigations into HAPH that we base many of our studies on today.

In the next article, Dr William K. Cornwell III from the University of Colorado and Dr Andrew Lovering from the University of Oregon discuss the cardiovascular and pulmonary physiologic responses to hypoxia and altitude. This outstanding review emphasizes clinically relevant changes that occur both acutely and chronically after going to high-altitude locations.

In our PHPN section, Amanda Schnell Heringer, RN, MS, and Elise Hazlewood, RN, MS, CCNS, walk us through the challenges of traveling at high altitude with PH. They discuss considerations needed regarding precautions, preparations, and altitude testing. They detail the precautions PH patients need to look out for when traveling by air; go into the preparations (including oxygen) patients should adhere to before traveling; and explain what types of testing are needed prior to going to high altitude. It is an excellent review of the up-to date recommendations.

Finally, in an extraordinary interview, Dr Bull spoke with Dr Peter Hackett of the Altitude Research Center at the University of Colorado. Dr Hackett is a world-renowned authority on altitude physiology and medicine with an unparalleled career and experience in high-altitude settings. The interview spans not only Dr Hackett's unique career path, but also how this field has unfolded in recent decades. Thank you to both Dr Bull and Dr Hackett for this contribution.

I know you will enjoy and learn so much from this issue of *Advances*. This exceptional issue will serve as a resource to so many regarding the fascinating field of altitude physiology and how it relates to our patient population.

#### Deborah Jo Levine, MD

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#### GUEST EDITOR'S MEMO

### The mountains are calling and I must go—John Muir

Likely for as long has mankind has walked this earth, the lure of the mountains has called to us. The satisfaction and joy of ascending our high peaks are known to many of us, but there is also a cost for climbing too high. This issue of *Advances in Pulmonary Hypertension* reviews some of the fascinating impacts of high altitude on the pulmonary vasculature. A great deal of our current understanding of pulmonary vascular physiology was derived from early clinical observations of the impact of altitude on the pulmonary arteries and right ventricular function. The ability to study, understand, and then modify these acute and chronic changes remains of great clinical importance as more and more of the population live and recreate at high elevations.

In the ensuing pages, Drs Jeff Robinson and Christopher Chang from the University of Oregon review the fascinating history of altitude research, taking us from early observations in animals through some of the early human studies which helped to unravel this complex physiology. Dr Andrew Lovering from the University of Oregon and Dr William Cornwell from the University of Colorado review the fascinating impacts of altitude on cardiopulmonary physiology and right ventricular function during exercise.

Amanda Schnell Heringer, RN, MS, and Elsie Hazlewood, MS, CCNS, walk

through some of the important clinical considerations for altitude-related travel in patients with pulmonary hypertension.

Lastly, Dr Peter Hackett takes us on the fascinating journey of his career in high-altitude medicine, reviewing his initial steps down this career path, some harrowing and life-threatening moments, and personal accomplishments and epiphanies along the way.

We hope the reader will be inspired to look further into this fascinating subject, and perhaps some young investigators starting their careers may discover the opportunists this field of investigation can offer.

#### Todd Bull, MD

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## From the Andes to the Rocky Mountains: A Historical View of High-Altitude Pulmonary Hypertension

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Division of Pulmonary and Critical Care Medicine Department of Medicine Oregon Health and Science University Portland, OR The current understanding of high-altitude pulmonary hypertension (HAPH) is largely attributable to the work of a small cadre of international scientists. The present article discusses the discovery and early investigations into HAPH that now serve as the foundation of our modern understanding of the disease. Further, though HAPH is clearly a distinct entity, we highlight how this early work led to a broader understanding of pulmonary vascular disease—including pulmonary arterial hypertension (PAH)—through the development of translational clinical models of disease, elucidation of hypoxic signaling, and therapeutics applicable to PAH.

#### INTRODUCTION

The recognition and early scientific investigation of high-altitude pulmonary hypertension (HAPH) is a relatively recent occurrence, with the discovery of HAPH in humans occurring in the mid-1900s. The foundation of our understanding of HAPH was laid by South American investigators working in the Andes, with further development by investigators working in the Rocky Mountains of Colorado. Together, this international team made groundbreaking observations that elucidated the effects of altitude on the pulmonary vasculature and risks to human health. Moreover, their work spurred countless other investigators to expand on our understanding of the effects of acute and chronic hypoxic exposure and the specific structural, cellular, and molecular underpinnings of the pathophysiologic changes seen in the diseased pulmonary vasculature. This has not only expanded our understanding of HAPH but has contributed greatly to our understanding and treatment of pulmonary arterial hypertension (PAH).

#### BRISKET DISEASE AND BEYOND: THE RECOGNITION OF PULMONARY HYPERTENSION IN ANIMALS

Early Investigations of the Relationship of Pulmonary Artery Pressure and Hypoxia The first invasive hemodynamic measurements of pulmonary arterial pressure (Ppa) were performed in 1852 in work by Carl Beutner.<sup>1</sup> He measured baseline Ppa in the dog, cat, and rabbit via thoracotomy and cannulation of the pulmonary artery with a monometer. Focusing exclusively on acute changes in Ppa, he ventilated the animals with bellows, observing that halting ventilation for an extended period of time caused an increase in Ppa. Since the experimental animals had undergone bilateral vagotomy, he conjectured that venous blood stimulated cardiac nerves, increasing the force of cardiac contraction, thereby increasing Ppa via an increase in cardiac output.<sup>2</sup> Over the next century, others investigated the effects of respiration on the pulmonary circulation, also demonstrating the early rise in Ppa with various methods of limiting ventilation. The trigger of this phenomenon was reviewed by Wood in 1902,<sup>3</sup> with the potential mecha-

nisms being "first, that it is due to a damming back of the blood; second, that it results from a greater flow to the right heart; third, that it is due to direct contraction of the arteries of the pulmonary circulation." It wasn't until 1946, and the work of Von Euler and Liljestrand, <sup>4</sup> that the modern concept of hypoxia having direct effects on Ppa was discovered. Their work sought to determine how pulmonary vessels react to variations in inhaled gases by ventilating cats with various concentrations of O<sub>2</sub> and CO<sub>2</sub>. The most striking finding was that while ventilating the lungs with 100% O<sub>2</sub> caused a small decrease in Ppa, subjecting the lungs to ventilation with  $10.5\% O_{2}$ caused a robust increase in Ppa. They also noted that this increase in Ppa was not associated with change in left atrial pressure, was larger than the increase in Ppa caused by moderate exercise (assumed to be due to increase in cardiac output), and was not prevented by vagotomy. Thus, they concluded that there was a direct constrictive action of hypoxia on the pulmonary vessels. The exact mechanisms by which hypoxia triggers (directly or indirectly) pulmonary vascular smooth muscle contraction and the possible contribution of pulmonary artery endothelial cells remain incompletely explained and continue to be an active area of investigation.

Key Words—high-altitude pulmonary hypertension, pulmonary arterial hypertension, brisket disease Correspondence: robinjef@ohsu.edu

Disclosure: Neither of the authors has any potential conflicts of interests to report.

#### The Discovery of Pulmonary Hypertension in Animals With Chronic Hypoxia Exposure

In the late 1800s, ranchers began moving their herds to the fertile grasslands around South Park, Colorado, situated in the Rocky Mountains at 2438 to 3048 m (8000 to 10000 ft). What appeared to be ideal grazing land for cattle proved to be deadly, with many dying of what the ranchers termed "brisket disease," after the characteristic swelling of the neck tissues that normally comprise the brisket cut. Rather than a scientific curiosity, initial investigations were motivated by the financial strain caused by loss of herds at altitude. In 1913, two prominent South Park ranchers contributed \$100 each to the Experimental Station at Colorado Agricultural College for the study of brisket disease. With this, George Glover and Isaac Newsom, a veterinarian and pathologist, respectively, began to explore the cause of brisket disease.<sup>5</sup> They noted the following:

During the winter of 1913–1914, one South Park stockman estimates that out of between four and five hundred cattle, he lost thirty calves and ten or twelve older animals. Another man lost 12 during the winter of 1912–1913. Still another says, after several years' experience, he has lost practically all bulls that he shipped in from a low altitude and he figures his loss at about five per cent.... While this may seem small, yet in the aggregate it means many thousands of dollars.<sup>6</sup>

In their investigations, they quickly excluded feed differences, communicable or infectious etiologies, and other environmental exposures, and determined that it was high-altitude exposure that led to weak pulses, distended neck veins, and edema. Moreover, when affected animals were transported to Denver (a mere 1585 m [5200 ft] elevation), the heart failure resolved. Zeroing in on heart failure as the trigger, they titled their manuscript "Brisket Disease (Dropsy of High Altitude)." With the work of Von Euler and Liljestrand not to come for another 3 decades, the connection between the pulmonary cir-

culation and right ventricular failure was understandably out of reach. However, it is impressive that in just 2 years, Glover and Newsom established the causative agent (altitude) of brisket disease, the resulting heart failure, the "cure" of transport to lower altitude, and also realized that using "native" highland bulls for breeding could improve hardiness. Research interest waned until the 1940s, when one of Newsom's students, Rue Jensen, established through histologic studies that the source of brisket disease was right heart failure, postulating that "atmospheric hypoxia causes pulmonary changes which lead to increased resistance to circulation through the lungs and failure of the right ventricle."

In the late 1950s, two young faculty members at the University of Colorado School of Medicine, Jack Reeves and Robert Grover, intrigued by their observations of pulmonary hypertension (PH) in children with congenital heart disease, began collaborating with Arch Alexander and Don Will, veterinarians at Colorado State University in Fort Collins with a newfound interest in brisket disease. Familiar with the work of Glover, Newsom, and Jenson, along with the acute effects of hypoxia on the pulmonary vasculature as established by Von Euler and Liljestrand, they sought to understand the effects of chronic hypoxia on the pulmonary vasculature. To do this, they established a laboratory on Mount Evans in the Rocky Mountains at an altitude of 3871 m (12700 ft). Here, they exposed young steers to chronic atmospheric hypoxia for 2 months, performing serial catheterizations demonstrating a marked increase in mean Ppa from baseline of 25 mm Hg to 75 mm Hg. Histologic examination demonstrated marked thickening of the media of the small muscular arteries, with pulmonary arteriograms showing similar findings. Noting that lambs were known to endure altitude with ease, they performed parallel hemodynamic studies that demonstrated that they did not develop PH at altitude.<sup>7</sup> Through this elegant experimental approach, the connection of HAPH with the pulmonary circulation was cemented, coupled with the idea that certain species were more prone to develop HAPH than others.

Later work reinforced the comparative biologic work that Grover performed in those early experiments. Noting the significant variability in rise of mean Ppa that Grover saw in his experiments, two scientists at Colorado State University tested the hypothesis that degree of susceptibility to HAPH was inherited. After 8 years of breeding bulls and heifers that were identified as either susceptible (hyperreactive) or resistant (hyporeactive) based on their degree of severity of HAPH, they had 2 to 3 generations of offspring and were able to clearly show that with exposure to hypoxia the hyperreactive or hyporeactive trait was preserved by selective breeding.8

#### THE DISCOVERY AND DESCRIPTION OF HAPH IN PERU

Much of what is known about HAPH in humans began with physiologic studies in the Peruvian Andes where the partial pressure of oxygen can be as low as 85 mm Hg.<sup>9</sup> In the late 19th century, French physiologists Paul Bert and François-Gilbert Viault first noted polycythemia in individuals resided in Morococha, Peru, a highland town that sits at an altitude of 4540 m (14895 ft) above sea level with a mean barometric pressure of 445 mm Hg. In 1921, Joseph Barcroft led an expedition of English and American physiologists to Cerro de Pasco, Peru, located at an altitude of 4330 m (14206 ft). Barcroft performed various physiologic experiments and measurements on his team while in Cerro de Pasco only to offensively and falsely conclude that residents of high altitudes are of lower physical and mental capacity based on his findings. In response to this claim, Carlos Monge Medrano also led an expedition to Cerro de Pasco in 1927 to evaluate cardiopulmonary physiology in the native population. Monge observed that high-altitude residents had polycythemia, increased blood viscosity, increased serum protein, and hyperventilated with a chronic respiratory alkalosis, which he called "La enfermedad de los Andes" or the "disease of the Andes."10 This condition was later named Monge disease or chronic mountain sickness (CMS). CMS has since been further characterized as a

syndrome seen in some residents living above 2500 m (8202 ft). Findings include hypoxemia, polycythemia, PH, and cor pulmonale, with symptoms similar to those of other chronic respiratory diseases. CMS symptoms have been shown to resolve once a person relocates to sea level for a sufficient period of time.<sup>11,12</sup>

Human pulmonary artery catheterization was then a novel technique, having first been performed in 1945 by Cournand in a subject with mitral stenosis and resultant PH.<sup>13</sup> By the 1950s, acute anoxia had been demonstrated to result in elevations in Ppa but the effects of chronic hypoxemia on the pulmonary circulation were still unknown. Rotta and colleagues<sup>14</sup> studied 4 groups of Peruvian men: lifelong sea-level natives, lifelong high-altitude natives, those who immigrated to high altitude 1 year prior to the study, and high-altitude natives with CMS. Performing the first hemodynamic studies demonstrating HAPH in humans, they found that Ppa and right ventricular (RV) pressures were elevated in all high-altitude groups compared with those at sea level. The rise in pressures was lowest in the immigrant group and highest in the CMS group. In the CMS group, Ppa and RV pressures slightly decreased with the administration of oxygen, but these changes were not seen in other groups. They postulated that this suggested that there were mechanisms other than hypoxic pulmonary vasoconstriction that led to the changes in the pulmonary circulation in long-term high-altitude residents with HAPH.<sup>14</sup>

In an effort to clarify the prevalence of HAPH, Penazola et al performed electrocardiographs and vectocardiographs of 1090 Peruvian natives ranging from newborns to 60 years of age. Of these, 650 were residents of Lima at sea level while 440 lived in Morococha. All newborns demonstrated evidence of RV hypertrophy (RVH), reflective of the right-heart-dominant circulatory system in utero. These findings resolved within a few weeks at sea level but persisted lifelong at high altitudes.<sup>15,16</sup> Following this, they performed a series of cardiac catheterizations in high-altitude newborns, children ages 1 to 5 years and 6 to 14 years, and men ages

17 to 34 years. Newborns at sea level and high altitude had an average mean Ppa of approximately 60 mm Hg. While the mean Ppa quickly normalized for newborns at sea level, the decline was much slower and remained elevated into adulthood for high-altitude residents. At high altitudes, the average mean Ppa was 45 mm Hg at ages 1 to 5 years, 28 mm Hg at ages 6 to 15 years, and 28 mm Hg in adults. In comparison, the average mean Ppa at sea level in adults was 12 mm Hg. Cardiac output, right atrial pressures, and pulmonary capillary wedge pressures were similar at different altitudes.17,18

During this period, fueled by the electrocardiographic work and hemodynamic studies, Arias-Stella and colleagues performed groundbreaking histopathologic studies that for the first time elucidated the pathogenesis of HAPH. To confirm the findings of the electrocardiographic studies, autopsies were performed to evaluate the hearts of residents of low and high altitudes who died of noncardiopulmonary causes. In total, 241 natives with ages ranging from newborn to 80 years of age were examined. All newborns had a greater right heart mass compared to the left heart. The left heart became dominant between the ages of 1 day to 3 months, although RVH was still present. The RVH resolved between 3 and 23 months at sea level but persisted to varying degrees in all age groups at high altitude. The left ventricular mass was similar for a given age group at low and high altitudes.<sup>19,20</sup> Hypothesizing that altitude altered the pulmonary vascular structure, they performed histologic examination of the distal pulmonary arterial branches of 30 subjects native to sea level and 20 subjects native to altitude-all of whom died in accidents or from acute noncardiopulmonary disease. The ages of the subjects ranged from newborn to 76 years, and they found that the newborns had no differences-all had the characteristic fetal pattern of increased smooth muscle cells in the small pulmonary arteries and muscularization of the arterioles. However, they found that children and adult subjects at altitude retained this phenotype, with thickened vascular walls and lumen narrowing in comparison to the sea level subjects.<sup>21,22</sup> For the first time, structural changes in the pulmonary vasculature were identified as the primary cause of HAPH, rather than polycythemia, cardiac output, or hypervolemia.

### PARALLEL SCIENCE IN THE ROCKY MOUNTAINS

The comprehensive work being done in South America was being published in local journals that were elusive to their North American counterparts who had been studying bovine HAPH. Hearing of the studies by Penaloza and colleagues, Grover traveled to Peru in 1961 and became fully aware of the extensive hemodynamic and histologic work they had performed.<sup>23</sup> Inspired by this, Grover and a cadre of physician-scientists from the University of Colorado sought to determine if there was evidence of PH at 3094 m (10150 ft) in Leadville, Colorado-the highest incorporated town in the United States, but also markedly lower in elevation than the 4572 m (15000 ft) of their Peruvian counterparts. Initially, an electrocardiographic study was carried out, wherein the entire high school population of 508 subjects underwent physical exam, chest radiograph, and electrocardiogram. In comparison to similar subjects from a lower altitude, they found an electrocardiographic preponderance of rightward deviation, suggesting RV enlargement.<sup>24</sup> This study was followed by a hemodynamic follow-up in 1962, where 28 healthy and asymptomatic individuals residing in Leadville who were 12 to 17 years of age underwent resting and exertional right heart catheterization. Sixteen of these children had 2 findings of PH-either on examination (increased P2), chest radiograph (enlarged pulmonary vasculature or right atrium), or electrocardiogram (right axis deviation)-while 14 had no objective evidence of PH. The results were striking in that 10 of the 28 subjects had a resting mean pulmonary arterial pressure  $(mPAP) \pm 25 mm$  Hg. Also notable was that, with exercise, many of the subjects had significant increases in mPAP that were exaggerated in comparison to subjects at sea level.<sup>25</sup> Interestingly, one of the subjects with particularly severe

PH in this study relocated to sea level, and after 11 months underwent repeat right heart catheterization, demonstrating normalization of resting Ppa<sup>26</sup> This reversibility was further studied by the South American group, where Sime et al<sup>27</sup> studied the effects of relocating high-altitude natives to Lima. The study included 11 young healthy male volunteers born around Cerro de Pasco with baseline studies performed in Morococha, then repeated after living in Lima for 2 years. They found that hypoventilation decreased but did not normalize and the heart rate decreased while the cardiac index increased. In addition, the mPAP and average pulmonary vascular resistance normalized. This normalization was not seen with supplemental oxygen alone, which further supported the primary role of structural remodeling in the pathophysiology of HAPH.<sup>27</sup>

#### RESULTING LEGACY AND CONTRIBUTIONS TO THE MODERN PARADIGM OF PAH

While the initial identification and understanding of HAPH was motivated by the economic interests of cattle farmers, an international group of scientists appreciated the potential impact of HAPH on human populations and dedicated their careers to this pursuit. By the mid-1960s, the South American investigators and Coloradoan counterparts firmly established the demonstrable increase in resting Ppa in both natives and newcomers to altitude, and that this was often associated with polycythemia and other findings of CMS. Further, they were able to show that in children born at altitude, the normal regression of RVH and pulmonary vascular smooth muscle with corresponding fall in pulmonary arterial pressure and resistance was aberrant and persisted later in life, establishing the histopathologic basis for HAPH. Finally, they established that exercise-even in healthy individuals-was accompanied by an intensified increase in Ppa and blunting of the normal exercise-related decrease in pulmonary vascular resistance.

This fundamental work led to decades of work elucidating the mechanistic underpinnings of altitude- and

hypoxia-induced alterations of the pulmonary vasculature, including the pathobiologic differences between acute hypoxic vasoconstriction, and the hypertrophy or hyperplasia of pulmonary arterioles and RV remodeling observed with chronic hypoxia and altitude exposure. Recognizing the interspecies variability in development of HAPH, reproducible rodent models of hypoxia-induced PH were developed, which along with continued application of the bovine model have greatly aided our mechanistic understanding of PH. These models recapitulate the remuscularization of previously nonmuscularized arterioles, along with hypertrophy of muscularized precapillary pulmonary arteries. Further, they also demonstrate vascular-specific inflammatory responses that have more recently been recognized as a driver of PH, with enhanced perivascular expression of inflammatory mediators and influx of neutrophils and macrophages.<sup>28</sup> These later developments also led to the discovery of vasoactive mediators that contribute to the vasoconstriction and remodeling seen in PH, including nitric oxide, prostacyclins, and endothelin. Recognizing the parallels with experimental PH and the human disease state of PAH, these have all served as therapeutic targets that have significantly improved symptoms and outcomes for those afflicted.<sup>29</sup>

While these discoveries led to the development of a greater understanding of the pulmonary circulation and undoubtedly led to enhanced understanding of PAH, HAPH demonstrates a distinct difference in comparison to the family of diseases that comprise World Health Organization group 1 PAH. As opposed to PAH, which is progressive, subjects with HAPH demonstrate reversibility when relocated to sea level. Further, PAH characteristically results in significant exertional limitation, while subjects with HAPH paradoxically demonstrated no apparent exercise limitations despite the increased RV afterload, hinting at a fundamental difference between those with HAPH and PAH—and a point of future studies that can be leveraged to further our understanding of both disease states.

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### Impact of Altitude on Cardiopulmonary and Right Ventricular Hemodynamics During Exercise

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#### INTRODUCTION

More than 100 million individuals travel to high-altitude environments per year for work or pleasure.<sup>1–3</sup> Reductions in the partial pressure of ambient oxygen initiate a cascade of physiologic responses, which place unique stressors on the cardiovascular and pulmonary systems. These stressors are accentuated by attempts to exercise. Information available on the effects of hypoxia on human physiology, both at rest and with exercise, is derived primarily from healthy individuals. Nevertheless, the prevalence of cardiovascular disease (~18 million), hypertension (~108 million), and heart failure (~6 million) in the United States is high, and many of these individuals, who have abnormal sea level (SL) hemodynamics, may experience much larger perturbations in cardiopulmonary and exercise hemodynamics than healthy populations. In this review, cardiac and pulmonary responses to hypoxia are emphasized, and exercise physiology at altitude is highlighted.

#### CARDIOVASCULAR, PULMONARY, AND RESPIRATORY RESPONSES TO HYPOXIA

The hemodynamic response to hypoxia is highly dynamic and evolves from

Correspondence: william.cornwell@ucdenver.edu Disclosures: None to report. Conveniences of modern travel allow for an increasing number of people to sojourn to mountainous, high-altitude locations for work and/or pleasure. Travel to these types of locations places unique stressors on the human body and, more specifically, the cardiovascular and pulmonary systems since ambient oxygen content declines at altitude. The physiologic response to hypoxia is a highly dynamic process that begins immediately and continues to evolve from acute (hours to days) to chronic (days to weeks) time periods. Furthermore, sojourns to hypoxic locations frequently involve exercise, which places additional strain on the heart and lungs. The aim of this review is to emphasize clinically relevant physiologic responses that occur, both acutely and chronically, after travel to high-altitude locations.

acute (hours to days) to chronic (days to weeks) exposure. Acutely, the cardiovascular response to hypoxia is dominated by a marked increase in sympathetic nerve activity (SNA).<sup>4–8</sup> Microneurography studies of healthy humans have demonstrated that SNA increased from SL values of  $27.1 \pm 2.9$  bursts/min to  $36.4 \pm 2.6, 39.1 \pm 3.1, \text{ and } 40.2 \pm 4.2$ bursts/min at 4000, 5000, and 6000 m, respectively.7 This increase in sympathetic tone results from hypoxia-induced activation of peripheral chemoreceptors and acutely increases heart rate (HR), stroke volume (SV), cardiac output (Qc), and muscle blood flow compared with levels encountered at SL.4,5 As the body adapts to hypoxia over several days to weeks, Qc falls in response to a decline in SV.<sup>4-6,9</sup> This reduction in SV occurs over the first several days of altitude exposure and stabilizes after ~1 week.6,10,11

Hypoxic pulmonary vasoconstriction leads to an acute increase in pulmonary arterial pressures (PAPs), which increase in proportion to altitude exposure.<sup>12-16</sup> In a study of healthy mountaineers, pulmonary artery systolic pressure, determined by echocardiography, increased from 22  $\pm$  3 mm Hg at SL to 33  $\pm$  6 mm Hg after 4 hours of exposure to a

simulated height of 4500 m (fraction of inspired oxygen  $[FIO_2] = 0.12$ .<sup>15</sup> In another study involving invasive hemodynamic assessment by pulmonary arterial catheterization of healthy volunteers, mean PAP increased from  $14 \pm 1 \text{ mm Hg}$  at a baseline altitude of 490 m to  $22 \pm 1$  mm Hg after only 10 minutes of breathing hypoxic gas  $(\text{FIO}_2 = 0.12).^{13}$  At more extreme altitudes, greater increases in PAP have been observed.<sup>16</sup> In Operation Everest 2, healthy volunteers experienced large increases in mean PAP from  $15 \pm 1$ mm Hg to  $34 \pm 3$  mm Hg over a 40day simulated ascent to 8840 m (summit of Mount Everest), and pulmonary vascular resistance increased from  $1.2 \pm$  $0.1 \text{ to } 4.3 \pm 0.3 \text{ Woods units.}^{16}$ 

Ventilation increases dramatically after hypoxic exposure. For example, among healthy males, resting minute ventilation increased from  $7.1 \pm 0.3$ L/min at SL to  $11.8 \pm 0.5$  L/min on the first day of exposure to 3110 m.<sup>17</sup> This increase in ventilation continues to rise over time with ongoing hypoxic exposure<sup>18</sup> and is relevant insomuch as a significant amount of oxygenated blood may be diverted to supply respiratory muscles to support the increased work of breathing, thereby causing a respiratory "steal" phenomenon which contributes to reductions in exercise capacity at altitude.18,19

#### CARDIOPULMONARY HEMODYNAMICS OF EXERCISE AT HIGH ALTITUDE

One critical relationship in exercise physiology pertains to oxygen uptake  $(VO_2)$  and Qc, such that Qc increases ~6 L/min for every 1 L/min rise in  $VO_2$ .<sup>20–22</sup> During exercise at high altitude, this relationship between Qc and  $VO_2$  is preserved.<sup>23</sup> However, maximal oxygen uptake  $(VO_2Max)$  declines in proportion to the altitude at which exercise is undertaken. Specifically, VO-2Max decreases by ~1% for every 100-m increase in altitude above 1500 m.<sup>24–26</sup> Ventilatory threshold, a marker of sustainable workload, occurs at HRs similar to SL but at lower workloads.<sup>26,27</sup>

During acute exposure to high altitude, exercise Qc may be higher than SL values in response to the aforementioned rise in sympathetic tone. However, as the body acclimates, exercise Qc typically declines compared with SL values.<sup>23</sup> Notably, this reduction in Qc is not a result of hypoxia-induced left ventricular (LV) dysfunction. In Operation Everest 2, it was found that SV was maintained for any given pulmonary capillary wedge pressure, indicating that LV contractility is preserved even up to extreme altitudes of 8400 m.9 At any level of work, HR is higher at altitude than at SL, but maximal HRs achieved at altitude are lower than exercise at SL.<sup>28</sup> Stroke volume at all levels of exercise is reduced compared with values during exercise at the same workload at SL.28

Exercise PAP at altitude is higher than levels observed at SL and therefore may impact right ventricular (RV) function,<sup>23</sup> yet less is known about RV performance during exercise at altitude. The majority of studies evaluating cardiovascular function have incorporated echocardiography,<sup>23,29-31</sup> and it is unclear whether observed changes in noninvasive metrics of RV performance (eg, strain, tricuspid annular plane systolic excursion [TAPSE]) result from changes in loading conditions or are a reflection of overt dysfunction.<sup>29</sup> In one of these studies, RV longitudinal strain at 5050 m was reduced compared with SL values, but this decrement in strain was attributed to reductions in RV volumes.<sup>29</sup> In Operation Everest 2, which

incorporated pulmonary arterial catheters, right atrial pressure (a surrogate marker of RV function) was reduced during rest and exercise at altitude, and based on this finding, it was concluded that RV function is preserved.<sup>9,16</sup> Nevertheless, in placebo controlled studies using either sildenafil<sup>32</sup> or bosentan,<sup>33</sup> pulmonary vasodilator administration with normobaric hypoxia resulted in a reduced PAP and pulmonary vascular resistance and was associated with an improved maximal exercise workload (FIO<sub>2</sub> = 0.10)(26) and a 30% increase in VO<sub>2</sub>Max (FIO<sub>2</sub> = 0.12)(27).

Additionally, there are data to suggest that RV function may decline over time in response to chronic (eg, weeks) exposure to hypoxia.<sup>29</sup> Hypoxia-mediated augmentations in PAP lead to an increase in RV afterload.<sup>6,34-40</sup> In a study of healthy individuals, RV end-diastolic volume increased from  $52 \pm 12$  to 61 $\pm$  25 mL at SL to 5085 m, respectively, which coincided with increases in systolic PAP (13.1  $\pm$  5.9 versus 26.6  $\pm$  10.8 mm Hg).37 In another study, TAPSE declined from 2.9  $\pm$  0.3 to 2.3  $\pm$  0.3 from SL to 5050 m.<sup>29</sup> Finally, pharmacologic reductions of PAP by administration of sildenafil led to an increase in LV SV.<sup>39</sup> In total, these data suggest that, as PAP (and hence, RV afterload) rises, RV contractility declines over time, and this reduction in RV function compromises LV SV. Further research incorporating invasive and comprehensive assessments of RV function-such as has recently been performed in patients with pulmonary arterial hypertension,<sup>41</sup> heart failure with preserved ejection fraction,<sup>42</sup> heart failure patients supported by LV assist devices,<sup>43</sup> and even healthy individuals exercising at SL<sup>40</sup>—is necessary to characterize the effects of acute and chronic altitude exposure on resting and exertional RV performance and how decrements in RV function may influence LV SV, Qc, and exercise capacity overall.

A minority of individuals experience subacute mountain sickness after several months' exposure to hypoxia at altitude. Subacute mountain sickness in humans has been compared to Brisket disease in cattle living above 3000 m, which was reported well over 100 years ago and presents as edema in the neck and chest.<sup>6</sup> In humans, this syndrome was described in soldiers who participated in vigorous exercises at altitudes of 5800– 6700 m for up to 6 months.<sup>44</sup> These individuals had evidence of RV failure, including generalized edema, ascites, and pericardial effusion. On echocardiography, these soldiers displayed evidence of RV enlargement, which normalized on repeat assessment several weeks after return to low altitude.<sup>44</sup> Based on these types of observations, it has been proposed that this disease entity be termed "high-altitude right heart failure."<sup>6,45</sup>

#### CONCLUSIONS

Sojourns to mountainous locations lead to acute and chronic stressors on the cardiovascular and pulmonary systems. These stressors result primarily from reductions in ambient oxygen content, which acutely increases sympathetic tone through activation of peripheral chemoreceptors and increases PAP through hypoxic pulmonary vasoconstriction. Hypoxia-mediated increases in RV afterload (ie, PAP) may lead to RV enlargement and compromise resting and exertional RV performance. Overt RV failure appears to be quite rare and occurs after several months of exposure to altitudes above 5500 m. Compared to SL performance, exercise capacity declines linearly in proportion to the level of altitude.

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### Up, Up, and Away: Clinical Considerations for Altitude-Related Travel and Pulmonary Hypertension

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# WHAT HAPPENS AT HIGH ALTITUDE?

High altitude is defined in the literature<sup>1,2</sup> as locations higher than 2500 m (8000 feet) above sea level. Increased altitude leads to lower barometric pressures, lower partial pressure, and lower inspired oxygen levels, leading to hypoxia. The body's attempt at homeostasis triggers increased ventilation, vasoconstriction of the pulmonary vasculature, systemic vasodilation, as well as increased heart rate, blood pressure, cardiac output, and hemoglobin. Importantly, pulmonary arterial pressures increase along with pulmonary vascular resistance at high altitudes. These effects are profound in patients with baseline pulmonary hypertension, as exposure to high altitudes can worsen hemodynamics, symptoms, and therefore result in short- and long-term negative sequelae.<sup>1-4</sup>

### PULMONARY HYPERTENSION AND HIGH-ALTITUDE TRAVEL

Due to the aforementioned pathophysiologic changes at high altitude, patients with known pulmonary hypertension should exercise caution when traveling to higher altitudes. However, many patients with pulmonary hypertension may still desire travel for pleasure, quality of life, and family or work obligations. It is important for patients and clinicians to be aware of risks of high-altitude travel and determine strategies to mitigate these risks. Current recommendations for travel to high altitudes in patients with known pulmonary hypertension include use of supplemental oxygen at altitudes greater than 1500–2000 m (4900–6500 feet) in any patient with WHO Functional Class 3–4 pulmonary hypertension, and it has been recommended that WHO Functional Class 3–4 patients avoid altitudes greater than 2000 m completely.<sup>1,3,4</sup>

### **COMMERCIAL AIR TRAVEL**

The effects of commercial air travel in pulmonary hypertension have been a growing area of interest, as many patients use commercial airlines for travel. Patients with pulmonary hypertension have varied tolerance during air travel and many can become hypoxemic in flight.<sup>5,6</sup> To minimize risk, supplemental oxygen while in flight is currently recommended for pulmonary hypertension patients with WHO Functional Class 3 and 4 and/or with those with arterial blood O<sub>2</sub> pressure <8 kPa (60 mm Hg).<sup>3,4</sup> Patients with known pulmonary hypertension should undergo high-altitude simulation testing (HAST) to determine their specific in-flight oxygen needs and plan accordingly to ensure adherence to airline policies and regulations to minimize travel interruptions.<sup>7</sup>

#### Key Words—high altitude, travel, pulmonary hypertension, COVID-19 Correspondence: claire.parker@ucsf.edu

Disclosures: Amanda Schnell Heringer is an Advisory Board participant for Actelion. Elise Hazlewood is an Advisory Board participant for United Therapeutics.

#### DETERMINATION OF MEDICAL STABILITY

Before high-altitude exposure, patients should be evaluated by their cardiologist or pulmonologist to ensure medical stability. Considerations for medical stability are important, and each patient has unique needs and recommendations regarding high-altitude exposure as related to WHO Functional Class.<sup>1,3,4</sup> Risks of airline travel and extended stay at high altitude should be reviewed clearly with patients to make an informed decision and prepare for emergency needs. Assessment of current hemodynamics and right ventricular function via right heart catheterization and transthoracic echocardiogram are valuable. Patients with baseline hypoxia and supplemental oxygen needs will likely have higher oxygen needs at higher altitudes. In addition to HAST, it is recommended to determine baseline needs for oxygen at rest and with exertion by performing 6-minute walk testing per American Thoracic Society standards.8 Additionally, overnight oximetry testing can evaluate current nocturnal oxygen needs, and clinicians can determine if altitude-related adjustments are indicated. If a patient is reporting significant symptoms, severe medication side effects, or is in process of medication titration, this may affect his or her ability to tolerate the increased demands of high-altitude changes.

These test results in addition to laboratory testing, physical examination, and symptom assessment can provide information on determination of clinical stability and risk for decompensation at altitude. High-altitude simulation testing can provide valuable information on individual oxygen needs.<sup>1,4,7</sup> Finally, when determining medical stability and recommendations for travel to high altitudes, clinicians should discuss goals of care and review education, including medication and supplemental oxygen adherence, and behavioral interventions, including diet, alcohol use, and effects of dehydration at high altitudes.

# ALTITUDE SIMULATION TESTING

High-altitude simulation testing is typically performed in a pulmonary function laboratory; testing protocols vary between centers. Use of a hypobaric chamber is an option for HAST, but these are not widely available.9 More commonly, HAST is administered with the patient wearing a tight-fitting mask and breathing air with 14%-15% oxygen (rather than 21%), to match the typical amount present in the pressurized cabin of an airplane at cruising altitude (equivalent to ~8000 feet).<sup>10</sup> A pulse oximeter continuously monitors the patient's oxygen saturation  $(SaO_2)$  as the supplemental oxygen level is adjusted to maintain the desired oxygen saturation (typical goal is  $SaO_2 > 90\%$ ). Oxygen saturation can also be confirmed by obtaining an arterial blood gas sample. It is recommended that patients planning to travel to high altitudes and/or via airplane undergo HAST testing at least 1 month before departure to allow for ordering and obtaining of oxygen equipment.

#### OXYGEN EQUIPMENT AND DOCUMENTATION FOR AIRLINE TRAVEL

Once oxygen requirements have been confirmed by testing, allow adequate time for obtaining insurance authorization and delivery of oxygen-related equipment. Per Federal Aviation Administration (FAA) regulations, US commercial airlines do not allow patients to bring their own oxygen tanks onto a flight (not in checked baggage, nor with them into the cabin). However, compressed oxygen can be used if provided by the airline.<sup>11</sup> Some airlines can directly provide the patient with oxygen for the flight, either free of charge or for a cost; patients can check with their airline if these services are available.<sup>12</sup> Some airlines do permit portable oxygen concentrators (POCs). Before travel, patients should check whether their oxygen company can provide a POC that is FAA approved and inquire about airline-specific policies regarding oxygen and batteries, including the process for boarding and disembarking, and required paperwork.<sup>12,13</sup> Due to the limited battery life of POCs, the patient may need to bring multiple charged batteries to last the duration of the flight. The general recommendation from the Pulmonary Hypertension Association (PHA) is to bring enough batteries to last 150% of the predicted length of the flight.<sup>13</sup> Battery life for POCs can be widely variable from 2 to 16 hours, depending on the machine itself, battery size, the oxygen flow rate, and whether oxygen flow is pulsed or continuous. Portable oxygen concentrator batteries contain lithium and must be packed in carryon baggage and cannot be in checked baggage per FAA regulation.<sup>11</sup> Patients should ensure they have access to oxygen tubing appropriate for the delivery system they will use in travel. If supplemental oxygen for travel is not approved by insurance, patients can pay out of pocket to rent the equipment for the trip.

Required documentation for flights can vary between airlines. Typically, a physician statement detailing the patient's medical need for oxygen is sufficient; however, some airlines will require specific forms to be completed for bringing medical equipment such as oxygen onto the flight.<sup>12</sup> Most airlines require notification of need for oxygen in flight at least 48 hours in advance. Allow adequate time to confirm documentation needs and submit completed forms. The PHA has multiple resources for patients and clinicians, including a template letter that can be provided for travel with oxygen or other medical equipment such as infusion pumps.<sup>13</sup>

#### **COVID-19 CONSIDERATIONS**

During the novel COVID-19 pandemic, travel is not recommended for groups at high risk for decompensation with COVID-19 infection.<sup>14</sup> However, some patients may choose to continue with

travel plans including airplane travel or to areas of high altitude. Due to current international travel restrictions, many patients are choosing to minimize air travel at this time, and travel by car has become more popular. While the need for in-flight oxygen is not an issue for these patients, considerations should be made if patients will drive through areas of high altitude or have a prolonged stay in locations above 1500 feet. Patients should continue to follow COVID-19 prevention precautions, including avoiding "hot spots" of high COVID-19 infection rates, adherence to hand hygiene, masking, social distancing, and minimizing contact with symptomatic individuals. Some locations require patients to quarantine for 14 days upon arrival, and this may affect access to oxygen equipment. Pulmonary function labs may require COVID-19 testing to be completed in a specific timeframe before having a HAST. Additionally, availability of some pulmonary function tests has decreased due to new COVID-19 protocols. As COVID-19-related guidelines are dynamic and change frequently, health care providers and patients should continue to review travel restrictions, precautions, and recommendations as provided by local health departments and the Centers for Disease Control and Prevention.<sup>14</sup>

#### RESOURCE AVAILABILITY DURING TRAVEL

The patient should be provided with contact information for a nearby pulmonary hypertension center or provider to contact if medical needs arise during travel. Depending on insurance, patients may need out-of-network care during travel, and a preauthorization may be beneficial to have in place before departure. If needed, the patient's oxygen supplier can work with insurance and arrange for oxygen equipment to be delivered to the patient's destination. This is especially important if the patient plans to travel in a high-altitude area.

#### CONCLUSIONS

Many patients with pulmonary hypertension identify travel as something that improves quality of life. Given the presence of the COVID-19 pandemic, additional considerations are needed regarding travel precautions in this patient population. Testing to determine oxygen needs for in-flight or prolonged high-altitude travel can inform decision making and treat high-altitude–induced complications. It is important for care teams to be aware of specific needs for patients with pulmonary hypertension who plan to travel to areas of high altitude to minimize risk and improve safety.

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### A Life at High Altitude: A Conversation With Todd Bull and Peter Hackett

In this special discussion for the PHA, Guest Editor Todd Bull, MD, spoke with Peter Hackett, MD, of the Altitude Research Center, Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Anschutz Medical Campus in Aurora, Colorado. Dr Hackett is a leading authority on altitude illness with years of experience in high-altitude settings both abroad and in the United States.

**Dr Bull:** It's a pleasure to be talking to Dr Peter Hackett, who is, without a doubt, one of the most renowned altitude researchers here in the United States, with a long and storied career. He has greatly contributed to what we know about the physiology and impact on humans as they ascend to higher and higher peaks. We're going to discuss aspects of his career and interests, exciting moments, and directions that we think the field is moving toward.

Dr Hackett, welcome. Let's start with a question about your early career. How did your work in altitude initiate? Where did your interest in the area stem from, and how early on did you find yourself investigating the physiology of high altitude in humans?

**Dr Hackett:** I've had a pretty unusual career. My love for the mountains is what propelled me into high-altitude medicine. That started at a young age when my grandparents took me to Colorado on a camping trip and I fell in love with the mountains. After medical school, I decided to go to San Francisco for my postgraduate training because it was close to Yosemite. Of course, during those years, I think I got 3 days off in my first year of training and was able to run up to Yosemite a couple of times.

After my internship year, I decided to take a break and went to Yosemite and became a helicopter rescue doctor. My training then was mostly in trauma and emergency medicine. I had a great summer fighting fires and doing rescues from this tiny helicopter. This was back in the mid-1970s, before it got very sophisticated.

One fellow I rescued, who had fallen on a climb and broken some ribs, owned a company called Mountain Travel, and he needed a doctor to go to Nepal with a trekking group for 3 months. At that time, I decided not to return to my medical training and went to Nepal. I ended up staying for most of the year, working as a volunteer doctor at this little aid post at 14000 feet on the way to Mount Everest. There were about 3 or 4 families in this tiny little village, and I stayed there for most of the year.

I saw all these people coming down with this weird virus on their way to Everest. When they got to about 14000 or 15000 feet, everybody started getting headaches and some nausea and vomiting, and they weren't sleeping and were short of breath. I couldn't understand what was going on until it finally dawned on me that this was altitude sickness. At that time, it was very little known. There was one paper in the *New England Journal of Medicine* from the experience of the Indian Army, Indira Singh, talking about altitude sickness, and that was about it.

I realized I was in a unique position to start collecting data and epidemiology and risk factors, and even treatment. I didn't quite know what I was doing, but I got a little help from John Dickinson, who was a British missionarv doctor in Kathmandu at the time. When I eventually came back to the States, I had this box full of questionnaires and physical exams, and I took it to Drummond Rennie in Chicago; he had published on high-altitude physiology and retinal hemorrhages and a little bit on cerebral edema. I collaborated with him, and we wrote up a paper, and it was the lead paper in The Lancet in 1976, called "The Incidence, Importance and Prophylaxis of Acute Mountain Sickness." That launched my career, really. I became published at the

age of 27 in a lead article, and it was a great opportunity. Then I had to make a decision about what I was going to do because I was developing a passion for the mountains and for altitude illness and keeping people safe.

I saw a number of deaths, and it really impressed upon me that perfectly healthy young people could go to altitude and die of pulmonary edema for no reason other than that they'd gone up a little too quickly. I was totally engrossed in this and decided I really needed to learn more about it. I approached Bob Grover and Jack Reeves, who were at the University of Colorado in the Cardiovascular Pulmonary (CVP) Research lab. They agreed to take me on as a fellow. A few months of that fellowship was taking them to Nepal to collect data and samples. We did hundreds of hypoxic ventilatory response tests manually with spirometry, and we had one of the early Hewlett-Packard ear oximeters, and we were able to do urine and plasma osmolality. We published a bunch of papers out of this research in Nepal, having to do with altitude illness.

With Grover and Reeves, I really learned about research, about how to critically review literature, how to do literature reviews, form hypotheses, how to test things, learned some statistics. That really was what launched my career in high-altitude medicine. After that, I worked clinically in emergency medicine and became boarded in emergency medicine, but I always had this interest in pulmonary physiology, especially the pulmonary circulation.

From there, I eschewed academic departments. It wasn't consistent with my lifestyle of going on expeditions every year as well as interests in field research. That took me to places like Mount Lo-

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gan in the Yukon with Charlie Houston, and I started a project at a 14000-foot camp on Mount Denali, funded by the National Institutes of Health, where we saw quite a few very ill climbers with pulmonary and cerebral edema. It was there that we did the first bronchoalveolar lavage in high-altitude pulmonary edema (HAPE) and also studied vasodilators for treatment. I was there for 8 summers. I was with John West and his American Medical Research Expedition to Everest in 1981, in which I summited Everest and collected data all the way to the top. We made quite a mark in the field of high-altitude physiology and published a large number of papers and a book that many of the American Thoracic Society people will be familiar with.

So that's how I got started. It was my love for the mountains and a burning intellectual curiosity. What is it about high altitude that causes people to develop these life-threatening conditions? How do we make high altitude a safer environment and practice clinical medicine in the mountains? It was a nice combination of a passion for wanting to help people as a physician and my love for the mountains and climbing activities and trekking.

**Dr Bull:** That's a fantastic story and intro, and actually, it highlights a couple of important points. One is that research favors the prepared mind. Here you were at a clinical station, and you noticed a series of events, this viral illness, and you decided to dig into it and developed questionnaires regarding it and looked into physical findings, leading to an important early publication. So your clinical observations and then curiosity launched this career.

The other fascinating aspect to me is that I imagine, after your fellowship, there was probably some pressure to move on to a junior faculty position and start writing grant awards and work your way up the academic ladder, but you followed your passion and went in a different direction that was highly productive and successful. Was that encouraged or discouraged? Did people say, "There's no way you'll stay in research if you go in that direction"?

**Dr Hackett:** I thought you might pick up on that as an academician. There are a lot of young faculty and trainees out there that, I'm sure, struggle with the pros and cons of academia. It's tough to be in academic research at a medical center and be both a clinician and a researcher. It was made clear to me at the CVP that a research track would involve junior faculty and writing grants such as an RO1 and being part of the Program Project Grant and advancing along the traditional academic track, but it was also clear to me that I wasn't really cut out for that. I had to spend time in the mountains, and a major expedition would take at least 3 months a year. I wasn't going to give that up.

Emergency medicine fit the best at that time because it was then a brandnew field, and it was easy to just leave a job and then come back and get hired again almost anywhere. The advantages of not being in an academic institution were that I didn't have all these meetings, didn't have to report to a dean or a chancellor. I could do my own thing and didn't have to be in committees. The disadvantage, of course, was that funding opportunities were more limited without university affiliation. I had to have institutional review board (IRB) approval, so I would always be affiliated with a university in some capacity so that I could use their IRB.

It's great if you have a colleague next door that you can talk to about the latest developments or hypotheses. That's tough when you're an outlier and not in an academic setting, but I was able to develop a good community of people I was working with in this field. If I had to do it all over again, I'm sure I would have been more productive if I'd stayed in academics. I'm sure I would have published more. I still have a lot of data I haven't written up, a lot of papers I haven't published yet. I probably would have been more efficient. On the other hand, I would not have had quite the same career enjoyment. There are definitely tradeoffs.

**Dr Bull:** What I tell my fellows, in talking about their careers, is that you have to find a passion, and then if you can build your research on the pas-

sion, that is the most successful way to contribute because it keeps your enthusiasm and excitement high. From my standpoint, it's about trying to find the balance between the clinical work many of us love, while also keeping the research going to help you answer the myriad questions that always arise when you are seeing patients, "keeping the prepared mind."

Then again, some will say you have to home in completely on research, but where the excitement comes, or the inspiration, is at the bedside, seeing the problems that occur and then trying to tackle them. It strikes me that you're saying you were doing what you loved to do but then saw clinical questions that would arise while doing that, though it's fascinating that you mention these sentinel papers, the *New England Journal* paper about altitude. Can you tell us a bit more about that? How did that come about and what data were you collecting?

Dr Hackett: So I'll put this into context. Studying humans at altitude, you can do chamber studies, where you put people into large tin cans for days or weeks at a time and reduce the pressure, which is very expensive and labor intensive but much more tightly controlled. You can do hypoxic gas studies, which are not exactly the same as hypobaric hypoxia, but it can be done, and you can do field studies, where you take humans to high altitude to study acclimatization. You can't ethically take people to high altitude to study pulmonary edema, but you can do what I did in Nepal and Alaska, which is sit by the trail and, as people come by sick, study them because they've already gotten themselves sick.

The Everest expedition, organized by John West, was funded by the National Institutes of Health and the Army and the American Lung and American Heart Association and National Geographic and all sorts of organizations. We had a large team. Our purpose was to study the process of acclimatization, especially cardiovascular physiology. This was in 1981. At that time, there were not really good noninvasive measurements of pulmonary artery pressure, but we did a lot of exercise, physiology, and metabolism, and we looked at sleep at altitude and weight loss and hemoconcentration and hemodilution and lots of different issues.

One of the primary measurements we made was the determination of blood gases near the summit. We didn't actually get a summit value, but we got end-expired alveolar samples with the use of a special instrument on the summit. We would breathe into this instrument, and it would fill a pre-evacuated aluminum ampule and then rotate it. You pulled a trigger to activate it. We collected end-tidal air, and we also made the first measurements of barometric pressure on the summit, which was higher than expected based on the standard atmosphere calculations; this helps explain how it could be climbed without oxygen at that time of year but also explains why it may be impossible to climb in winter, since the pressure is at the very limit of human hypoxic tolerance, and the barometric pressure and PIO<sub>2</sub> are significantly lower in winter.

We were there in October, and like you'd expect, on all of these trips, whether it's Denali or Mount Logan or Everest or Kilimanjaro, there's always risk. There's always inherent risk in going to that kind of altitude and subjecting yourself to that kind of weather. We had a pretty tough time, and there was a lot of attrition; at the end of the trip in October, we still hadn't gotten to the top with our measurements. We had done a lot of good work at base camp at 18000 feet and in the Western Cwm at 21000 feet. At 21000 feet, the average oxygen saturation is in the high 70s, lower 80s, and we were doing fine despite that.

I was one of the few people left that still had enough stamina or drive toward the end of the trip to try for a summit bid. There were two of us, Chris Pizzo, a pathologist from Denver, and me, and two Sherpas. We set out for the summit and had a bit of an epic time. I ended up going to the top by myself because the Sherpa who was with me thought he was getting frostbite on his toes, so he turned around. Chris and his Sherpa were far ahead of me, and I couldn't catch up, so I ended up going by myself.

In those days, there were no ropes. It wasn't like it is now, with a rope all the way up to the top. It was a bit dangerous. Chris and his Sherpa made it to the summit, and on the way down they ran into me. I had just gone out of oxygen, and I said we should probably all go down together for safety. Chris said, "Peter, when are you going to be this close to the summit again?" I said, "Well, I'm out of oxygen." It turned out his Sherpa had hardly used any oxygen at all. He gave me an oxygen cylinder, and I continued up alone, making measurements. For example, my respiratory rate off oxygen was about 60, and on oxygen, it was more like 30 or 40, with tidal volumes at 2 L. The amount of hyperventilation is extreme. Based on the measurements we made, in these kinds of extreme hypoxic environments, the body chooses to defend alveolar PO<sub>2</sub> rather than defend pH. My pH, for example, was 7.57, with a PCO<sub>2</sub> of 7.5 and an arterial PO<sub>2</sub> of 24 or 26; extreme hyperventilation allows a shift in the oxygen dissociation curve to the left and loads more oxygen at the lung, which is beneficial.

I vividly remember getting to the summit after a bit of difficulty on the Hillary Step, which is a technical aspect of the climb. It's an 80° steep rock feature about 40 feet high, just below the summit. This is where there's often a lot of trouble, and we didn't have any fixed lines, but I was able to surmount it and realized two things: I was going to get to the summit because there's nothing else difficult on the way, and secondly, I might not ever be able to tell anyone about it because I had no radio and could possibly die on the way down. It's much harder to downclimb something like that than it is to climb up it.

I summited, and since I was by myself, I had to have a picture to prove I was there. I took a picture looking down on the north side just a bit. It was quite cold and windy, as you would imagine, and it was getting dark, about 4:30 in the afternoon, so I had to get out of there. On the way down, sure enough, I fell. I was headed for about an 8000-foot fall off the Hillary Step when my legs got caught behind a little piece of rock, and I was flipped upside down. It was a terrible situation. I was able to eventually right myself after doing what seemed about 10 sit-up attempts. I got my ice axe in a little piece of ice above me and then was able to work my way down to the bottom of the Step to Chris, who had been waiting for me a couple thousand feet lower down. We made it back to high camp together.

I hadn't had anything to drink at all that day because my water bottle was in my pack, frozen solid, and I couldn't put it inside my vest because I had all this monitoring equipment. I had a Respitrace and electrocardiogram (ECG) monitors and whatnot. That night, I had a hard time breathing. I started rehydrating and thought I had HAPE because I was in acute respiratory distress, and I thought I was going to die. I ended up coughing up a cast of my bronchial tree. Chris, being a pathologist, said, "Oh my God, that's one of the best bronchial casts I've ever seen!" I had this huge mucus plug that had compromised my ventilation, obviously. Once that cleared up, then I could settle down and survive the night and eventually the trip down to base camp. That was definitely one of my closest calls. I really felt like I should have died from the fall, and I was very, very lucky. John West is forever grateful that I didn't die because it would have ruined the whole expedition.

**Dr Bull:** [laughter] I'm glad he had his priorities in line there. That's quite a harrowing story. You really had an ECG monitor track what your heart rate was when you were hanging upside-down doing sit-ups on the Hillary Step?

Dr Hackett: It was very interesting. As you ascend to higher altitudes, the maximum heart rate drops, and the resting heart rate increases. The ability to do work is severely compromised at onethird barometric pressure, which is what the summit of Everest is. My maximum heart rate was about 132 at that altitude. It was almost 200 back home. When I fell, it didn't get much above that, but my resting heart rate was about 120, so I could only do about 12 heartbeats of work. Of course, it has to do with cardiac output, not just heart rate. The ECG showed a right bundle branch block, which I don't have at lower altitude. Interestingly, I was in an altitude chamber

at Duke with Richard Moon and Peter Wagner doing a study with a Swan-Ganz catheter at 16000 feet simulated altitude on a bicycle at max exercise, and I developed a right bundle branch block, and they thought it might have been the catheter hitting my right ventricle or some sort of iatrogenic thing, but then I went back and reviewed my ECG from Everest, and sure enough, I had a right bundle at 28000 feet as well.

**Dr Bull:** Did you say you were actually getting arterial blood gases on this ascent and doing arterial sticks as you were climbing to these high altitudes?

**Dr Hackett:** Actually, we didn't do arterial sticks. We collected a venous blood sample on the South Col at 26000 feet before going to the summit, and then we did the alveolar gas samples. Those were taken back to San Diego and analyzed along with controls. We feel that the data are quite reliable. We rushed the venous samples down to the blood gas analyzer at Camp 2, at 21000 feet, and then calculated the other values.

Subsequent to our expedition, Mike Grocott and his crew in a project called Xtreme Everest did do arterial sticks at around 27700 feet. They couldn't do them on the summit for logistical reasons. They published their studies in the *New England Journal* because it was so unusual, and they found the exact same things that we did: PCO<sub>2</sub> values less than 10 and arterial PO<sub>2</sub> values from 19 to about 28, and pH of 7.55 or so. It confirmed our data, and I have to hand it to them for doing femoral artery blood sticks under those circumstances.

**Dr Bull:** That's brave, being that high and letting someone poke your femoral artery, as well as hauling all that equipment up. Now that was the data that your group published in *Science* and other publications as well?

**Dr Hackett:** Yes. It actually ended up appearing in a few places. John West was the first author on many of those, and he also published a book called *Everest: The Testing Place*, altogether we published about 40 papers from the expedition. **Dr Bull:** What other peaks have you climbed as part of expeditions?

**Dr Hackett:** I've done clinical research to the summit of Mount Kilimanjaro with volunteers, doctors' groups mostly, and Pikes Peak in Colorado. That's not an expedition because you can drive right up there, but it has advantages since you can get there so quickly; people get reliably ill. Other expeditions were to South American peaks, Aucanquilcha to study the world's highest living humans, and Denali in Alaska, where we did a huge project. We flew in there with military airlift support every year on May 1 and came off every July 1. We'd be there for 2 months. Rob Roach from the University of Colorado and I did that together. We were able to get quite a bit of work done there. We looked at the effect of nifedipine on pulmonary artery pressure in people with HAPE and controls. We almost killed people by testing nitrates in HAPE, which turned out to be a very bad idea. We tested beta blockers in HAPE, which is also not a good idea. Brownie Schoene did the first bronchoalveolar lavage in HAPE patients. Ben Levine from University of Texas Southwestern flew in with Medtronic's echocardiography device, and the quartz crystal quickly froze, so we had to get a new one airdropped and take better care of it [laughter]. Denali is such an extreme environment; the low daily temperature was typically -40° in May and -25°F in June. It's 62° north; it's the highest polar mountain in the world, so a lot of our time was spent trying to survive. We had to build igloos to stay out of the wind, and we had very, very ill patients that we had to take care of, but it was all very exciting and productive, as was the Mount Logan project with Charlie Houston in the '70s. We would fly onto Mount Logan at 17500 feet, some directly, and others would stage the ascent to avoid getting severely ill. One of our studies from there was published in the New England Journal. The background was interesting. I flew into 17500 feet directly, and that night, we monitored my oxygen saturation with the Hewlett-Packard ear oximeter and found incredible desaturations into

the 50% and 60% level. The next night, I took acetazolamide (Diamox), and we found that it almost totally eliminated the severe central sleep apnea and the periods of severe hypoxemia. In the New England Journal article, the graph showing the 2 sleep traces—one on acetazolamide and the other without it—is of my oximetry study. You know, that was a very dangerous operation; there were plane crashes. Fortunately, nobody was killed, but flying and landing on a glacier at 17500 feet is radical. Charlie was very bold, as was John West. These were very risky expeditions, and we were really lucky that nobody died.

Nowadays, well, you may be familiar with the big altitude chamber that just opened up in Bolzano, Italy, where you can control the wind, the temperature, the humidity; you can make it snow. You can take people to 30000 feet in a highly controlled environment. Obviously, it's a much safer thing to do. For the future, however, for those who are interested in high-altitude medicine, I think the field is really wide open. If your interest is in pediatrics or neurology or obstetrics or trauma, there is so much that can be done in terms of both clinical and basic research.

There's the bench research, obviously, looking at basic mechanisms, and look what's happened with Hypoxia Inducible Factor (HIF) biology, which had a lot to do with high-altitude work. There is the clinical work with either hypoxic gas breathing in animal models or humans. There's the hypobaric hypoxia exposures, either in a chamber or in the field. There is so much to be learned about people living at high altitude here in Colorado. We still don't know the prevalence of pulmonary hypertension due to the altitude in our resort communities. We don't know the prevalence of central sleep apnea and, in general, sleep-disordered breathing in these communities. We don't know about the relationship between sleep-disordered breathing and pulmonary hypertension. We don't know how many people have to leave the mountains because they just get breathless and lose their exercise capacity as they age, and we don't know the exact mechanisms involved there, but I take care of a lot of those people,

and some of them I send to you at the University of Colorado Pulmonary Vascular Disease program for workups to look at their pulmonary circulation. There's a lot to be done, and if your passion is any of these things that could be combined with high altitude, or you'd like to be in the mountains, then it can be a great combination.

**Dr Bull:** What other advice do you have for those entering the field now?

**Dr Hackett:** The best advice I can give is to get the best training possible, to start with, and find the best mentors available. It's not easy. There are not many people doing high-altitude research, and there's not a lot of funding for it, so it takes motivation to go after the funding sources and find the right mentors and get the necessary experience.

Clearly, if one is going to do research, they need some training in research methodology and statistics and all that goes along with it. My advice, if someone is really serious about making a contribution by doing clinical or basic research, is to really buckle down and get some training in research before trying to do it or while establishing themselves.

**Dr Bull:** What are the major obstacles right now in terms of investigative work or research in the field?

**Dr Hackett:** Major obstacles, as with other areas, have to do with funding opportunities. High-altitude medicine has been a bit of an orphan field. It probably hasn't gotten a lot of respect in the past. It's more respectable now, but it has to overcome this perception that doctors who do high-altitude research are just looking for an excuse to go play in the mountains. The way to get around that is with solid foundations in research and really good, quality work because there is some truth to that criticism.

That's why I make a plea for getting really trained in research. That's one obstacle in addition to funding; and then there's the time it takes for field studies, the dangers, the problems with IRBs. You can't ethically get people critically ill with HAPE, but you can take care of them if they get it on their own, if you are in the right spot at the right time, which is where my work came in and why fieldwork was successful.

Hypobaric facilities are also very expensive and limited. Hypoxic gas studies are a great way to go because they can be much less expensive and give you much more control, but we still haven't worked out the exact differences between hypobaric and normobaric hypoxia. That's a great study in itself.

For a person who wants to get involved in this field, they need to find a chairman of their department, or senior faculty, who shares the interest or can at least get enthusiastic about high-altitude medicine. It's very difficult to go into a department where you don't feel supported or you don't feel that there are like-minded people. There are not many places doing high-altitude research currently. A young investigator needs motivation and passion to get it going and develop their own program and break trail, as we say in the mountains.

**Dr Bull:** And where do you think the biggest opportunities are right now? What do we really need to understand or know right now in the field, if you could focus a research question?

Dr Hackett: The current important questions range from molecular biology to epidemiology. One could take their pick, but one of the more fascinating things is HIF biology. Humans at altitude offer a great model because they're perfectly healthy, just hypoxemic. It offers great opportunities. The Holy Grail in high-altitude medicine in some aspects is to find breakthroughs by using these models of healthy humans at altitude or sick humans at altitude for your work in the intensive care unit (ICU). That really hasn't materialized. HIF is obviously a link. There's a lot of genetic work going on, looking at the relationships of illness at altitude and acclimatization and people with acute respiratory distress syndrome and survival and that sort of thing and finding common genetic patterns. That's one big area, formulating a question you might have

from the ICU and figuring out how you could use humans at altitude as a model to help answer that, a common factor being hypoxemia.

Then you've got whole population studies. You've got hundreds of thousands of people living above 7000 feet in Colorado and very little information on what happens to their blood pressure, for example, and what's the best medication for control. Is atrial fibrillation really more of a risk living at 8000 or 9000 feet than at sea level? Nobody knows. I get calls all the time from cardiologists around the country, and there is not a reliable answer. There's a tremendous amount of important work to be done, helping people live healthier in the mountains so they can enjoy their chosen lifestyle, or helping those in ICUs or at sea level with hypoxic diseases or anemia or other problems of oxygen transport. Those are two main themes.

**Dr Bull:** I think understanding the physiology of hypoxia and pulmonary vascular disease at altitude could certainly help solidify what we're doing or help point us in new directions for helping those who get hypoxemic or develop pulmonary vascular diseases.

Dr Hackett: I think another idea for a research project is looking at whether exaggerated physiologic pulmonary hypertension is a limiting factor in exercise performance at high altitude. I'm convinced from my clinical practice that hypoxic pulmonary vasoconstriction or physiologic high-altitude pulmonary hypertension can cause a decrement in exercise performance in certain people and that, if you relieve it with pulmonary vasodilators, exercise can markedly improve. I'm talking about people living in Summit County or in Telluride. Such a study has never been done. The only studies to date in hypoxia or high altitude with phosphodiesterase inhibitors, for example, were not in selected patients complaining of impaired exercise performance, only in nonselected subjects, and they showed no real benefit on average. It's still an important clinical question ripe for research.

**Dr Bull:** I'd also like to get your thoughts on COVID-19. There were statements to the effect that this was like HAPE, something where altitude could inform us. I'd like to get your view on whether or not that is the disease state we're looking at with COVID hypoxia.

Dr Hackett: There has been some literature and a lot of discussion about whether COVID-19 pneumonia is the same as HAPE. Obviously, they're both noncardiogenic pulmonary edema with severely impaired gas exchange. There are similarities, but the pathophysiology is entirely different; one is a hydrostatic edema due to exaggerated hypoxic pulmonary vasoconstriction with patchy or uneven vasoconstriction, as far as we understand, and the other is a viral infection with inflammation and maybe loss of hypoxic pulmonary vasoconstriction in areas with resultant shunting, or perhaps with vascular thrombosis as well.

My colleagues and I published articles on that, and Eric Swenson and Steve Archer and others have also addressed that. As for treatment, the best therapy for HAPE is oxygen, and it's also valuable in COVID-19 pneumonia for improving oxygenation, but while oxygen resolves HAPE, since it reduces pulmonary vascular resistance, pulmonary artery pressure, and edema formation, it does not address the pathophysiology of COVID-19 pneumonia. Suggestions that pulmonary vasodilators that are useful in HAPE might be useful in COVID-19 pneumonia or acute respiratory distress syndrome are dubious at best and potentially dangerous. I think where the altitude community has failed the clinicians on the front lines is in helping them recognize that, like at high altitude, these severely hypoxemic patients may not be hypercapnic and may not need mechanical ventilation, but rather correction of the hypoxemia with oxygen therapy, at least initially. In addition, these patients may be tolerating hypoxemia better than expected because they have had some time to "acclimatize" to it, similar to persons at high altitude. I think with COVID-19 patients, if it takes more

than 3 or 4 days to slowly develop hypoxemia, they could tolerate it pretty well as long as they're not hypercapnic and they're not in true respiratory failure. Clinicians with altitude experience are accustomed to seeing people with  $SpO_2$  values in the 70s and 80s, levels of hypoxemia that may be entirely normal for the inspired  $PO_2$  for the altitude and without clinical adverse effects. Obviously, there are differences, and COVID-19 patients have other organ system involvement, but understanding the extent to which people can tolerate hypoxia is helpful.

I think clinicians in New York and other places at sea level don't have that experience of seeing people that are hypoxemic and are fine. They're used to seeing hypoxemia associated with hypercapnia, respiratory failure, loss of neuromuscular activity, or severe chronic obstructive pulmonary disease or other things. I do think that the altitude community should be better informing these clinicians. It's just the fact that humans can tolerate hypoxemia; give them oxygen, and you don't necessarily need to intubate them. Does that make sense?

**Dr Bull:** Yes. The global critical care society I think has evolved to watching from how we have treated acute respiratory distress syndrome in the past; the decision to intubate is made based on looking at the patient and taking in information, whereas when COVID-19 first hit, although there was much discussion after seeing what was rolling out of China, not knowing what we were dealing with led to intubating much earlier. I think there have been investigators and clinicians across the country looking at that again.

I do think it's an important point. If I can go back to the early days of COVID-19 and say, "Hey, we didn't necessarily need to put them on the vent when they hit 8 L of oxygen or 10 L of oxygen," part of that, too, was that we were trying not to put on heated high-flow or CPAP, BiPAP because we worried about aerosolizing the virus and putting others at risk, but we learned that the protection to ourselves was okay. One last question I was going to ask is, looking back, what are you most proud of to date?

Dr Hackett: I think increasing the awareness and improving the safety with respect to altitude illness for people going into the mountains. My paper in The Lancet in '76 was seminal, and it brought attention to a wide readership that perfectly healthy people do get sick when they go to the mountains, and they can die. At that time, there were a lot of deaths. Through research, publications, lecturing, through helping to found the Wilderness Medical Society and the International Society for Mountain Medicine and running the International Hypoxia Symposia, I feel that I've really helped to make going to altitude safer for people around the world, not just for mountain climbers, but for skiers and workers and everybody visiting or living at altitude.

I think I also turned the attention from respiratory physiology to the brain in the '90s when I started writing about the pathophysiology of mountain sickness, and since then, research has focused on what's going on in the brain, not just oxygen transport. Being a thought leader in the field has been rewarding. I feel good about what I've been able to offer in that respect. One of my guiding ideas is that people are going to help save the environment, to save our forests and our mountains, only if they get out there, enjoy these spaces, and love the experience. People protect what they love.

In terms of regrets, I don't know what researcher doesn't regret not getting projects across the finish line into publication. There are still unpublished studies in the queue. More importantly, maybe because I wasn't in academia, I didn't develop a cadre of young physicians or researchers coming up in this field to take over and continue with clinical as well as basic high-altitude research. There are many young docs wanting to get into the field, and there aren't many opportunities now for lack of strong programs at academic centers, and that's probably my main regret. If I had been in academics, we could've developed, hopefully, a strong program with a lot of

younger people coming up in the field, but there are still myriad opportunities and interesting applications. Being an expert in high-altitude medicine opens all sorts of doors; professional sports groups that are going to play at altitude and need advice, for instance. I have been a consultant with NASA on space sickness and published with Jim Bagian the only paper on cerebral blood flow and space sickness. I consulted on high-altitude ballooning projects, including the world's first nonstop around-the-world balloon flight and the first nonstop flight around the world in an unfueled aircraft, as well as a hang glider expedition to Everest, and many other interesting efforts. For all these fascinating things taking place at high altitude, people are looking for expertise in high-altitude medicine. One of them was the world's best rock and roll band going to play in South America wanting advice on dealing with the altitude; that got me hooked up with them, and I've been one of their doctors now for many years. That's been a gas, as they say in the rock and roll business. You never know; it's fascinating how the world of high-altitude medicine can take you so many places.

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